

# **Drug Challenges: Indications, Procedures, Risk, and Safety Outcomes**

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# Disclosures

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# Lecture Objectives

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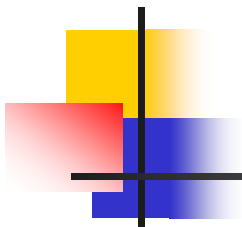
- To understand the difference between a drug challenge and an induction of drug tolerance procedure
- To develop a rationale approach to selection of patients appropriate for drug challenges
- To be able to design a drug challenge protocol
- To gain an understanding of the safety of drug challenges



# Outline

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- Terminology and Definition
- Indications
- Protocols
- Risks and Safety Outcomes



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# Drug Allergy: An Updated Practice Parameter

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology.

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**Ann Allergy Asthma Immunol 2010;105:273e1-e78.**



# Terminology & Definition

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# Terminology

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- Drug Challenge
  - Drug provocation test
  - Graded dose challenge
  - Incremental challenge
  - Test dosing



# Definition of Graded Challenge

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- *Graded challenge* or test dosing describes administration of progressively increasing doses of a medication until a full dose is reached.
- The intention of a graded challenge is to verify that a patient will not experience an immediate adverse reaction to a given drug.
- The medication is introduced in a controlled manner to a patient who has a low likelihood of reacting to it.





# Definition of Graded Challenge

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- Unlike procedures that induce drug tolerance, graded challenges usually involve fewer doses, are of shorter duration, and are not intended to induce drug tolerance.



# Induction of Drug Tolerance vs. Graded Challenge

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- Where there is a definite medical indication for the medication in question, either induction of tolerance or graded challenge procedures may be considered
- The choice of procedure depends on the history of the previous reaction and the likelihood that the patient is presently allergic to that agent



# Induction of Drug Tolerance vs. Graded Challenge

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- The goal of **induction of drug tolerance** is to modify an individual's biologic response to a given drug to allow treatment with it safely
  - **Intended for patients known or highly suspected to be allergic to the drug**
- The purpose of a **graded challenge** is to cautiously administer a drug when there is no intention to alter the patient's biologic response
  - **Intended for patients who are unlikely to be allergic to the drug**



# Indications

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## Summary Statement #70

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The objective of graded challenge is to cautiously introduce a drug in patients who are unlikely to be allergic to it. Unlike induction of drug tolerance, it does not modify a patients response to a drug. (D)



# Common Indications for Drug Challenges

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- To exclude a drug allergy in patient's with histories that are unconvincing
- To exclude cross-reactivity of structurally related drugs
- To exclude cross-reactivity of non-structurally related drugs to reassure patients (e.g. multiple drug allergic patients)



# Contraindications to Drug Challenges

<b>Autoimmune Diseases</b>	<b>Drug Induced Vasculitis</b>
Bullous pemphigoid	Leukocytoclastic vasculitis
Pemphigus vulgaris	Churg Strauss
Linear IgA bullous disease	<b>Organ Specific Drug Reactions</b>
Drug induced lupus	Cytopenias
<b>Neutrophilic Dermatoses</b>	Hepatitis
AGEP	Nephritis
Sweet's syndrome	Pneumonitis
<b>Severe Cutaneous Drug Reactions</b>	<b>Serum Sickness</b>
SJS/TEN	
DRESS	
Exfoliative Dermatitis	



# Indications for Drug Challenges

<b>Drug</b>	<b>History/Scenario</b>
cephalosporin	Patient with immediate reaction to cephalosporin who needs cephalosporin with dissimilar side chain
cephalosporin	Patient with penicillin allergy who needs cephalosporin
carbapenem	Patient with penicillin allergy who needs carbapenem
local anesthetic	Patient with history of local anesthetic allergy who needs local anesthetic

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78.





# Protocols

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# Drug Provocation Tests

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- Study from Montpellier, France evaluated patients with histories of immediate reactions (urticaria, bronchospasm, anaphylaxis, exanthems etc.) to a variety of drugs
- Performed beta lactam skin tests and then graded challenges
- Excluded patients with TEN/SJS/DRESS, organ specific reactions (e.g. hepatitis) and positive beta lactam skin tests

Messaad D et al. Ann Intern Med 2004;140:1001-6.



# Provocation Protocols

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- Cefazolin
  - 1, 5, 25, 100, 500, 2000
- Ibuprofen
  - 1, 5, 20, 80, 150, 300
- Clarithromycin
  - 1, 5, 25, 100, 500, 1000
- Ciprofloxacin
  - 1, 5, 25, 100, 500



# Positive Drug Challenges

<b>Drug</b>	<b>n</b>	<b>% Positive challenge</b>
Beta-lactams	416	8
aspirin	199	47
NSAIDs	161	27
paracetamol	118	17
macrolides	102	14
quinolones	33	27
other	343	7
<b>Total</b>	<b>1372</b>	<b>18</b>

**82% of challenged patients had negative challenges**



# Positive Reactions to Provocations

<b>Symptom/Sign</b>	<b>%</b>
urticaria	66.4
maculopapular eruption	9.1
bronchospasm	7.9
anaphylaxis without shock	7.0
anaphylaxis with shock	5.4
laryngeal edema	4.1



# Caveats of Drug Provocation Data

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- No selection of patients with immediate drug reactions
- Recent histories of reactions?
- Not placebo controlled



# Non-Immediate Beta-Lactam Challenges

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- 146 subjects referred for evaluation of non-immediate reaction to beta-lactam
- Drug provocation tests performed
  - 5 and 50 mg doses hourly
  - 100, 250, 500 mg at 48 hr intervals
  - Observed for 1<sup>st</sup> 8 hrs of drug administration then followed with a pager



# Non-Immediate Beta-Lactam Challenges

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- 22 subjects had positive challenges
  - 12 urticaria
  - 10 maculopapular exanthem
- No significant adverse reactions to challenges reported
- Only 2/22 (9%) had positive delayed intradermal test and patch tests





# Designing a Protocol

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# Considerations for Drug Challenges

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- Is the drug truly needed (no suitable alternative)?
- Was the reaction suitable for doing a drug challenge?
- Available tests lack high negative predictive value?
- What is individual risk-benefit?



# Considerations for Performing a Drug Challenge

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- Protocol to be used
  - Starting dose
    - Severity of reaction
  - Dose frequency
    - Immediate vs. delayed reaction
  - Observation
    - Immediate vs. delayed reaction
  - Duration of drug therapy
    - Delayed reaction
  - Oral vs. parenteral vs. topical
    - Drug dependent



# Considerations for Performing a Drug Challenge

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- Setting

- Outpatient vs. inpatient
- Appropriate supervision
- Appropriate medical equipment

- Need for placebo

- Multiple drug allergy
- Anxiety of patient
- History of subjective symptoms



# Determining the Starting Dose for a Graded Challenge

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- **Unlikely** patient is allergic
  - e.g. childhood history of rash to penicillin
  - Consider starting at  $1/100^{\text{th}}$  or  $1/1000^{\text{th}}$  of final dose
- **Very unlikely** patient is allergic
  - e.g. history of penicillin allergy in need of carbapenem
  - Consider starting at  $1/10^{\text{th}}$  of final dose



# Determining the Starting Dose for a Graded Challenge

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- **Complete confidence** that patient is not allergic
  - e.g. history of headache after taking penicillin
  - Administer full dose to negate history



# Graded Challenge: # of Steps

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- Number of steps in the procedure are much less than IDT procedures
  - e.g. 2-3 steps in graded challenge (as opposed to 12-14 steps for IgE mediated desensitization)
  - It is possible that a “graded challenge” consisting of more than 4 or 5 steps may induce modifications of immune effector cells and therefore induce tolerance in the patient
    - for that reason, future administrations of the drug should be given cautiously



# Graded Challenge: Dosing Interval

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- Time interval between doses
  - dependent on the type of previous reaction, and procedure may take hours or days to complete
- History of possible IgE mediated reaction
  - e.g. remote history of hives to cephalosporin
  - Consider dosing every 30 minutes with 1 hr final observation period
- History of delayed reaction
  - e.g. history of exanthem to a statin
  - Consider dosing every few days to allow time for reaction to develop





# Non-immediate Drug Provocation

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- Example protocol for beta-lactam
  - 1/100<sup>th</sup> dose
  - 1 week later 1/10<sup>th</sup> dose
  - 1 week later full dose



# Considerations for Performing a Drug Challenge

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- Comorbid factors

- Asthma, urticaria, eczema, viral illness
- General health

- Medications

- Drugs that may cause false negatives
  - Bronchodilators, drugs with antihistamine activity, systemic steroids, leukotriene modifiers
- Drugs that may worsen reaction
  - ACE-I, beta-blockers



# Potential False Interpretations of Drug Challenge Results

<b>False Positive</b>	<b>False Negative</b>
Anxiety reaction	Anti-allergic medications
Underlying disease (e.g. asthma)	Dose or duration of drug inadequate
Drug-induced exacerbation of underlying disease (e.g. chronic urticaria)	Inadvertent induction of drug tolerance (desensitization)
	Missing co-factor



# Placebo Controlled Drug Challenges

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- The choice of performing an open vs. a placebo controlled challenge is based on reaction type and patient characteristics
- Clinical features suggestive of needing a placebo challenge
  - Subjective symptoms of drug allergy (e.g. pruritus)
  - Anxiety level of patient regarding challenge to particular drug
  - Multiple drug allergy patients



# Placebo Controlled Drug Challenges

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## ■ Techniques

- Opaque capsules
- Inert filler
- Multiple placebos in highly anxious patients
- For history of delayed reactions, consider full day of placebo followed by active drug on separate day



# Symptoms with Placebo

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- Study of 56 inpatients undergoing drug provocations to a variety of medications
- 21 underwent testing with placebo
- 43% had symptoms with placebo
  - Palpitations
  - Restlessness
  - Sweating
  - Lump in throat sensation



# The “Nocebo” Effect

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- The nocebo effect is the onset of untoward reactions following the administration of an indifferent substance
- Italian study of 600 patients being evaluated for adverse drug reactions
- 27% occurrence of nocebo effect
- Majority of symptoms subjective
  - Emesis, urticaria, blood pressure changes also seen



# Risks & Safety Outcomes

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# Risks of Drug Challenges

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- Drug challenges do carry an inherent risk
- Risk varies considerably for drug challenges due to several factors
  - Prior reaction history
  - Specific drug
  - Type of challenge procedure



# Reactions to Drug Challenge: Unselected population

18% of patients had positive challenge

Relatively unselected population of patients with drug allergic reactions

<b>Symptom/Sign</b>	<b>%</b>
urticaria	66.4
maculopapular eruption	9.1
bronchospasm	7.9
anaphylaxis without shock	7.0
anaphylaxis with shock	5.4
laryngeal edema	4.1



# UT Southwestern Experience with Drug Challenges

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- Retrospective evaluation of safety of drug challenges
- Indications for drug challenges
  - Evaluation by A&I service to determine if drug challenge indicated
    - Not all patients challenged
  - Low pretest probability of drug allergy to implicated drug (majority)
  - Determine quinolone cross-reactivity
  - Reassurance for anxious patients



# Safety of Select Drug Challenges

Total Number of Patients	79
Total challenges	96
Age (mean)	51.6 years
Gender	Female: 76% Male: 24%
Setting	Outpatient: 82% Inpatient: 18%
Type of challenge	Open: 86 SBPC: 10
Single (Full Dose)	11 (11.4%)
Two Doses (1/10 <sup>th</sup> then full dose)	12 (12.5%)
Three Doses (1/100 <sup>th</sup> , 1/10 <sup>th</sup> , then full dose)	73 (76%)



# Safety of Select Drug Challenges

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- 79.2% challenges had no symptoms
- 20.8% challenges resulted in subjective symptoms only during early steps of challenge
  - All of these subjects tolerated full dose without symptoms suggesting that symptoms not a manifestation of drug allergy
- 7/10 patients had symptoms with placebo
- 100% tolerated full dose of drug without symptoms



# Safety of Select Drug Challenges

Symptoms During Challenges	# Challenges	Physical Findings
None	76	none
Lightheadedness with normal blood pressure readings +/- nausea	7	none
Tongue, lip, and or throat swelling	5	none
Nasal Congestion	3	none
Pruritus	2	none
Local Flushing	2	none
Tremulous	1	none



# Safety of Drug Challenges

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- Performing drug challenges in selected patients with low pre-test probability of being allergic appears safe
- Allergic reactions with drug challenges much more common in unselected drug allergic populations
- Symptoms frequent with drug challenges
  - Subjective symptoms may require placebo testing for confirmation



## Summary Statement #145

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To exclude the rare possibility of an IgE-mediated reaction to **local anesthetics**, skin testing and graded challenge can be performed in patients who present with a reaction history suggestive of possible IgE-mediated allergy to these drugs. (B)





# Local Anesthetic Challenges

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- Prick test with undiluted local anesthetic (LA)
- Subcutaneous challenge every 20 minutes with:
  - 0.1 ml 1:100<sup>th</sup> (1%)
  - 0.1 ml 1:10 (10%)
  - 0.1, 0.25, 0.5, 1.0 ml Full strength
- 236 patients evaluated by this method with all negative challenges
- Recommend testing with preservatives



# Local Anesthetic Challenges

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- Prick test with undiluted local anesthetic (LA)
- Intradermal test with 0.04 ml of 1:100 dilution of LA
- Subcutaneous challenge with 1.0 ml saline
- If placebo challenge negative after 20 min., 1.0 ml undiluted LA subcutaneous injection



# Local Anesthetic Challenges

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- 287 patients evaluated by this method
  - 3 positive skin tests (all tolerated pure lidocaine)
  - 9% reported subjective symptoms
    - Lightheadedness, anxiety, headache, pruritus etc.
  - No objective signs of adverse reaction occurred in any patient after challenge
- Recommend if positive skin test, repeat and if still positive, challenge with pure lidocaine and avoid methylparabens



# Conclusions

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- Drug challenges are an important tool in diagnosis and management of drug allergic patients
- Drug challenges can be used for patients with histories of both immediate and delayed drug allergic reactions
- With careful assessment of patients and appropriately designed protocols, drug challenges can be safely performed